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(54) A therapeutic preparation having ammonium nitrate as its active substance.

(57) Compressed tablet consisting of solid ammonium nitrate and auxiliary tabletting substances, with a coating.

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A THERAPEUTIC PREPARATION HAVING AMMONIUM NITRATE AS ITS ACTIVE SUBSTANCE.

The invention relates to a therapeutic preparation having ammonium nitrate as its active substance.

Ammonium nitrate is known as an agent that lowers the pH, so that the conditions for the forming of renal calculi and infections of the urinary tract are much less suited.

In general a solution of ammonium nitrate in water is used for this purpose; which solution can easily be prepared, due to the good solubility of ammonium nitrate, and is stable. Said solutions have a highly disagreeable taste.

Many attempts have been made to process ammonium nitrate to preparations which do not show this objection, e.g. by adding flavourings to solutions of ammonium nitrate. However, no flavourings have been found which sufficiently disguise the highly unpleasant taste of ammonium nitrate.

It has now been invented, that ammonium nitrate can be compressed into tablets with the commonly used auxiliary substances and that by coating these tablets with coating substances, coated tablets are obtained, which do not have the unpleasant taste of ammonium nitrate.

Thus a prejudice has been overcome; until now it was generally assumed that ammonium nitrate could not be compressed into tablets because of the known explosive nature of ammonium nitrate.

The preparation according to the invention is therefore characterized in that it comprises a compressed tablet consisting of solid ammonium nitrate, and auxiliary tabletting substances with a coating of lacquer or sugar.

It is suitable that each coated tablet contains 250 to 1000 mg of ammonium nitrate.

The manufacture and coating of the tablets is carried out in the usual way and with commonly used auxiliary substances.

Auxiliary tabletting substances are e.g. filling agents, binding agents, agents which stimulate disintegration of tablets, and lubricating agents.

Examples of such agents are:
starch, originating from patatoes, maize, rice or otherwise, lactose directly compressable or not calcium compounds, directly compressable or not, micro crystalline cellulose, glucose, saccharose, mannitol, sorbitol, colloidal, silicon dioxyde, talcum, magnesium stearate, cellulose derivatives, cross-linked polyvinyl pyrrolidon (PVPP).

Combinations of micro crystalline cellulose and anorganic auxiliary tabletting substances, e.g. colloidal silicon dioxide or talcum are very suitable, because with these substances tablets can be manufactured to the level of hardness which gives the best results when coated.

Preferably one should start from a mixture of ammonium nitrate, micro crystalline cellulose, colloidal silicon dioxide and a lubricating agent, e.g. magnesium stearate.

The ratio of the auxiliary components is chosen in a usual way, for instance 5% - 50% micro crystalline cellulose, based upon NH_4NO_3
0.05% - 10% colloidal silicon dioxide, based upon NH_4NO_3
0.1% - 2% lubricating agent, based upon NH_4NO_3.

Preferably the amount of micro crystalline cellulose should be between 17.5% and 22.5% and the amount of colloidal silicon dioxide between 0.1% and 0.3%, both based upon NH_4NO_3, because this gives the best results for tabletting.

The preparation of the starting mixture and the process of compression must be take place in a dry surrounding because of the hygroscopic nature of ammonium nitrate. Preferably said processes should take place in air with a relative humidity of at most 40%, or rather of 30% - 35%.

Compressing to tablets should preferably take place under a pressure that ensures that the tablets formed have a hardness of at least 15 kp, as measured by the Heberlein hardness tester. In this way tablets are obtained which are suitable for final coating.

For coating the usual substances can be used, such as methacryl compounds, waxes and resins (synthetic or non-synthetic), cellulose and its polymers, particularly cellulose acetopropionate (CAP), shellac etc. In particular lacquers which protect the coated tablets for a long time form the influence of acids (gastric acid) give a very good result.

The coating can have the usual thickness. A layer of acid resistant lacquer equivalent to 2 mg to 10 mg per cm^2 surface of the tablet is very suitable.

The invention is elucidated by means of the following example.

Example

In a room with a relative humidity of 35% 10 kg of ammonium nitrate was rubbed through a sieve which has a mesh width of 2 mm and mixed with 1.82 kg micro crystalline cellulose, (Avicel pH 102^R) and with 60 g colloidal silicium dioxide (Aerosil ^{R}) in a mixing vessel for 20 minutes.

Thereupon 120 g of magnesium stearate was added and the whole was mixed again for a few ~~of~~ minutes.

From the mixture thus obtained convex tablets were prepared having a diameter of 11 mm, and containing 500 mg of ammonium nitrate per tablet. The hardness of the tablets was 20 kp, measured by the Heberlein hardness tester.

Said tablets were then provided with a coating.

For this purpose they were put into a coating pan, whereupon they were sprayed in the usual way with a suspension of:

acid resistant coating lacquer (Eudragit L 12.5 p^R)	2624g≙328g dry substance
dibutylphthalate	16g≙ 16g dry substance
pigment suspension	3334g≙1000g dry substance
1:1 mixture of acetone: isopropanol	8026g
	14000g≙1344g dry subatance

The pigment suspension consisted of:

talcum	560 g
magnesium stearate	80 g
titane dioxide	480 g
polywax 6000 (33% dispersion in water)	240 g
isopropanol	2640 g
	4000 g with 30% solid substance

The tablets were provided with a coating layer with a weight of 20.5 mg/cm^2.

The dry substance content originating from the lacquer was 5 mg/cm^2.

The coated tablets were tested for their resistance against gastric acid according to USP XX with artificial gastric juice pH 1.2.

The coating layer lasted for 60 minutes.

The coated tablets were also tested for their behaviour in artificial intestinal juice (according to USP XX, pH 7.5).

In this artificial intestinal juice they disintegrated after 6 to 7 minutes.

CLAIMS

1. Therapeutic preparation having ammonium nitrate as its active substance, characterized in that it comprises a compressed tablet of solid ammonium nitrate and auxiliary tabletting substances, with a coating or dragee layer.

2. Preparation according to claim 1, characterized in that it contains 250-1000 mg of ammonium nitrate per tablet.

3. Preparation according to claim 1 or 2, characterized in that in the tablet micro crystalline cellulose, colloidal silicon dioxide and a lubricating agent are present as auxiliary tabletting substances.

4. Preparation according to claims 1-3, characterized in that
5% - 50% micro crystalline cellulose
0.05% - 10% colloidal silicon dioxide
01.% - 2% lubricating agent
are present in the tablets, based upon ammonium nitrate.

5. Preparation according to claim 4, characterized in that
17.5% - 22.5% micro crystalline cellulose
0.1% - 0.3% colloidal silicon dioxide
are present in the tablets, based upon ammonium nitrate.

6. Preparation according to any one of the preceding claims, characterized in that the tablet has a hardness of at least 15 kp, measured by the Heberlein hardness tester.

7. Preparation according to any one of the preceding claims, characterized in that the coating consists of an acid-resistant lacquer.

8. Preparation according to claim 7, characterized in that the coating layer consists of 2 mg to 10 mg (per cm^2 of the tablet surface) of acid-resistant lacquer.

9. Process for preparing a therapeutic preparation according to one of the preceding claims, characterized in that ammonium nitrate and auxiliary tabletting substances are mixed in an atmosphere with a relative humidity of at most 40%, and the mixture is compressed in the usual way into tablets which are provided with a coating in the usual way.

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EUROPEAN SEARCH REPORT

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Application number

EP 85 20 0870

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
A	CHEMICAL ABSTRACTS, vol. 79, no. 6, 13th August 1973, page 216, no. 35091p, Columbus, Ohio, US; F.S. HOM et al.: "Soft gelatin capsules. I. Factors affecting capsule shell dissolution rate", & J. PHARM. SCI. 1973, 62(6), 1001-6 * Abstract *	1-9	A 61 K 33/02 A 61 K 9/28
A	FR-A-2 201 086 (J. MADIER) * Page 2, lines 1-13; claims 1-3 *	1-9	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11-09-1985	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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L : document cited for other reasons

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